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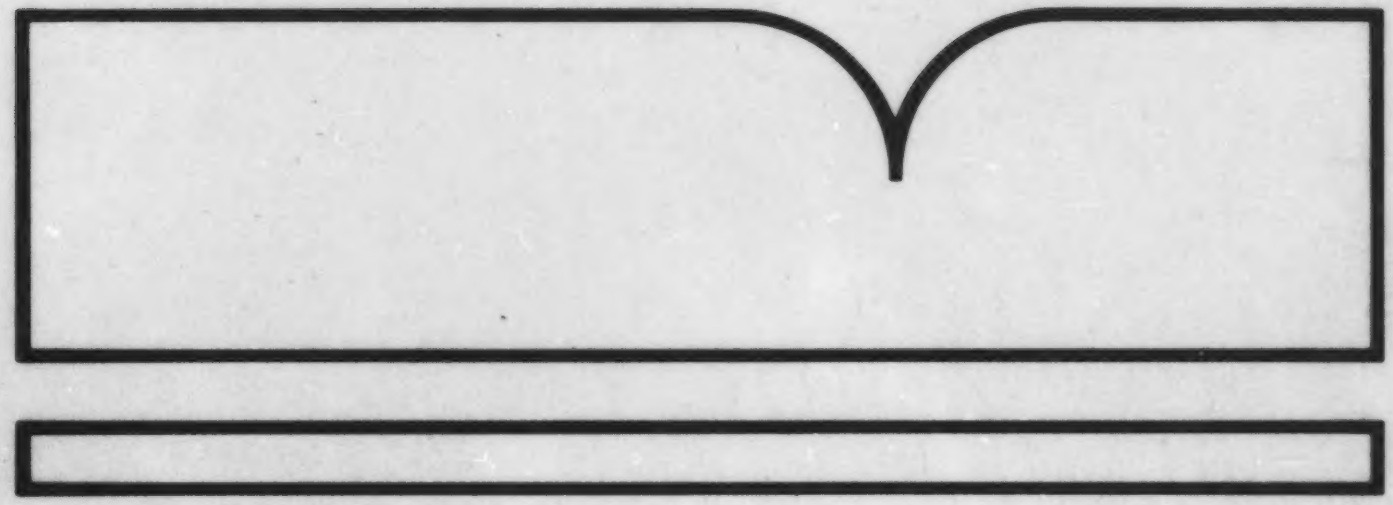

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16. ABSTRACT

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Pulmonary Function Adaptation to Ozone in Subjects with Chronic Bronchitis

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Twenty smokers with chronic bronchitis were exposed to 0.41 ppm ozone for 3 hr-day for 5 consecutive days and reexposed 4 days later to determine (1) if they are sensitive to ozone, (2) if they adapt, and (3) if the adaptation lasts longer than 4 days. There were significant decrements in forced vital capacity (FVC) and forced expiratory volume in 3 sec (FEV_3) on the first day of the 5-day repeated exposures and also on reexposure 4 days following cessation of the sequential exposures. Symptoms experienced were mild and did not predominate on any exposure days. These results suggest that individuals with chronic bronchitis adapt rapidly to ozone and lose this adaptive phenomenon within 4 days. The small decreases seen in FVC and FEV_3 ($\leq$3%) appear to impose no more than minimal limitations on their daily activities.

INTRODUCTION

People with chronic respiratory diseases have been considered to be at higher risk for development of adverse pulmonary effects when exposed to oxidant pollution. Studies of normal subjects performing light-to-moderate exercise have found that the threshold dose of ozone (O_3) for ventilatory function decrement is between 0.20 and 0.30 ppm (Farrell *et al.*, 1979; Folinsbee *et al.*, 1980; and Dimeo *et al.*, 1981). In two separate studies, subjects with chronic obstructive lung disease exposed to 0.12 and 0.20 ppm O_3 were found to have no significant change in ventilatory function, although small decreases in arterial oxygen saturation were seen (Linn *et al.*, 1982; Solic *et al.*, 1982). Asthmatic subjects showed no significant decrement in pulmonary function when exposed to 0.2 ppm O_3 (Linn *et al.*, 1978). In another study, although one-third of the subjects with asthma showed decrement in pulmonary function when exposed to 0.25 ppm, the group as a whole did not show a significant change (Silverman, 1979).

Normal subjects show adaptation to the effects of ozone after repeated intermittent exposure to levels of about 0.4 ppm. This adaptation can be lost within 4 to 7 days if the subjects are not reexposed (Kulle *et al.*, 1982). A recent study showed that some people never adapt completely or lose their adaptation very quickly (Linn *et al.*, 1982).

Adaptation to ozone and its loss may have practical significance in patient counseling. Ambient O_3 levels in excess of 0.4 ppm have been recorded in Southern California for 5 successive days (California Air Resources Board, 1979). Individuals living in areas with high levels of pollution may be less sensitive to

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the effects of ozone than those in low pollution areas (Hackney *et al.*, 1977). While previous studies have shown that a few individuals are unusually sensitive to ozone (Horvath *et al.*, 1981; Linn *et al.*, 1982), studies designed to investigate adaptation in subjects with specific respiratory diseases have not been done. The present study was designed to investigate the ventilatory response of subjects with chronic bronchitis intermittently exposed to 0.41 ppm ozone, 3 hr/day for 5 days, then reexposed after 4 days.

MATERIALS AND METHODS

Subjects. Twenty subjects with chronic bronchitis were recruited from Baltimore City and the metropolitan area through want ads in a local newspaper. All volunteers underwent a screening examination that included a medical history, physical examination, 12-lead electrocardiogram and baseline spirometry. Volunteers were accepted if they fulfilled the following criteria: (1) productive cough on most days for a minimum of 3 months in the year and for at least 2 successive years; (2) airflow obstruction as defined by a FEV_1/FVC ratio of <75% and/or a FEV_3/FVC ratio of <95%; (3) FVC ≥80% of predicted (Morris *et al.*, 1971) to exclude subjects with restrictive disease; (4) history of cigarette smoking for at least 10 yr with a present rate of one pack per day; (5) normal resting electrocardiogram; (6) no allergies; (7) not on medication; and (8) no hypertension, cardiovascular disease, or pulmonary disease (except chronic bronchitis) by history or physical examination. Subjects with a history of asthma and/or wheezing were excluded.

Approval was obtained from the Human Volunteers Research Committee of University of Maryland prior to commencement of the research. Informed consent was obtained from all volunteers and all received financial compensation for their services. Characteristics of the 20 subjects who completed the study are given in Table 1. No one withdrew because of symptoms. The mean FEV_1/FVC ratio was 73% and the mean FEV_3/FVC ratio was 89%. Reversibility of the airways obstruction was not evaluated.

Exposure facility and protocol. The study was conducted in an environmentally controlled chamber, restricting environmental pollutants to O_3. Air entering the chamber was passed through high efficiency particulate absolute (HEPA) filters and activated carbon filters, permitting cleanliness approaching class 100 (<100 particles/ft^3 ≥0.5 μm or <3534 particles/m^3 ≥0.5 μm). The ventilation rate of 8.49 m^3/min (300 cfm) in the 22.2 m^3 (784 ft^3) exposure room enabled a complete air change every 2.6 min. Temperature was maintained at 22.2 ± 0.5°C (72 ± 1°F) and relative humidity at 50 ± 1%. All room air was exhausted to the outside without recirculation, enabling positive control of the O_3 concentration during the exposure periods. A more detailed description of the environmental chamber was presented in a previous publication (Kerr, 1973).

The ozone was produced by passing 100% oxygen through a water-cooled silent-arc ultraviolet O_3 generator and introduced via stainless-steel tubing into the exposure room of the chamber through the room air input diffuser. The ozone concentration in the chamber was continuously monitored by a Mast microcoulomb O_3 sensor (Model 724-5), a Monitor Labs Chemiluminescent O_3 monitor

TABLE I
SUBJECT CHARACTERISTICS

Subject No.	Sex	Age (yr)	Height (cm)	Weight (kg)	Smoking history		Screening values	
					packs/day	No. of yr	FEV_1/FVC,%	FEV_1/FVC,%
1	M	51	180	70	1½	36	56	75
2	M	30	157	77	1–2	13	77	93
4	M	42	196	102	1–1½	30	58	83
5	M	48	175	70	1–1½	25	71	90
6	F	34	168	75	1	19	77	90
7	F	39	168	72	2–3	28	82	93
8	M	44	188	77	1½	30	57	78
10	M	38	175	78	1½–2	24	76	91
11	M	36	170	66	2	20	79	91
15	M	31	185	86	1½	16	71	89
16	M	45	185	64	2	20	78	92
19	M	48	178	73	1½–2	31	81	92
20	F	39	155	67	1½	22	78	92
21	M	41	185	75	2–3	30	72	91
22	M	41	163	80	2–3	20	75	90
23	M	49	163	73	3–4	32	74	90
30	M	33	183	82	2	16	73	91
31	M	31	183	82	2	17	72	89
32	M	35	175	77	2	18	82	93
33	M	33	180	75	2	20	70	91

(Model 8410), and a Dasibi Ultraviolet O_3 photometer (Model 1008-PC). Daily calibration checks were performed with a Monitor Labs Model 8500 permacal or, once it was on line, the Dasibi O_3 photometer. The monitors were also calibrated on a monthly basis with another Dasibi O_3 photometer belonging to the State of Maryland Air Management Administration. The mean concentration of the exposures was 0.41 ppm with a range from 0.39 to 0.46 ppm.

The subjects were exposed between November and April when the ambient O_3 levels were at their minimum. The highest 1-hr average O_3 concentration for Baltimore City during this period was 0.06 ppm, and the monthly averages of the daily 1-hr maximums ranged between 0.01 and 0.03 ppm.

The study was conducted over a 3-week period with each subject acting as his or her own control. The subjects breathed filtered air for 3 hr/day on Thursday and Friday of Week 1 (Control Days), were exposed to 0.41 ppm O_3 for 3 hr/day on Monday through Friday of Week 2, and on Week 3 breathed filtered air on Monday, then were reexposed to 0.41 ppm O_3 on Tuesday. Two control days were performed to obtain a more realistic control value for each subject, since the degree of obstruction may vary from day to day. Reexposure 4 days after the 5-day sequential exposure was chosen based on a previous study with nonsmokers (Kulle *et al.*, 1982).

The subjects were studied in groups of two to four. All subjects were asked to abstain from smoking 2 hr prior to entering the chamber and were confined to the Class 100 clean room 1/2 hr prior to each control and exposure period. All control and exposure measurements were conducted at the same time each day. Every day, 1 hr prior to conclusion of each exposure and control period, bicycle ergometer exercise was performed at a work load of 100 W (612 kg-m/min) at 60

rpm for 15 min. This exercise increased minute ventilation ($\dot{V}_E$) by approximately four to five times the resting $\dot{V}_E$. Two subjects (Nos. 20 and 22) had the workload decreased to 80 W because of muscle fatigue.

Measures of responses. Spirometric measurements were performed daily at the conclusion of each control and exposure period using a 10-liter Stead–Wells spirometer. A Collins Eagle I microprocessor was interfaced with the spirometer to ascertain at the time of testing that the forced vital capacity (FVC) maneuver exceeded the criteria set forth by the American Thoracic Society (ATS Statement, 1979). Three or more maneuvers were performed until at least two technically acceptable tracings were obtained. The FVC, and forced expiratory volumes in 1 sec (FEV_1) and 3 sec (FEV_3) were manually calculated from the spirogram and were recorded as the data for analysis. All volumes were expressed in liters adjusted to BTPS.

Ozone is readily perceived by odor at 0.41 ppm, and all subjects knew which days were exposure days. At the end of each exposure day, the subjects were asked if they could sense a change in symptoms associated with the exposure. These symptoms were recorded on a questionaire by one of the investigators.

Data analysis. Tukey's test was used for multiple comparisons of means (Tukey, 1949; Huntsberger and Leaverton, 1970). The standard error term for the tests was derived from a repeated-measures analysis of variance (Keppel, 1973). The means of the subject data from each day of Week 2 (Exposure) or Week 3 (postexposure/reexposure) were compared with the average of the 2 control days of Week 1 to obtain a mean difference for that day. Numbers for statistical significance were obtained by dividing the mean difference by the standard error, and comparing the results with the significance levels in Tukey's test. A level of $P = 0.05$ was used to establish statistical significance. Use of the average of the 2 control days for comparison was justified, since no significant differences in pulmonary function were observed between these 2 days using the Tukey's test.

RESULTS

Statistical analysis of the data from the 20 subjects with chronic bronchitis is shown in Table 2. On the first day of ozone exposure there were significant decreases in both FVC and FEV_3. On the second through fifth exposure days no significant differences from control were observed. When the subjects were reexposed to ozone 4 days after the sequential exposures, significant decreases in FVC and FEV_3 were again seen. Although no significant changes were observed in FEV_1, small decreases were seen on the exposure days in a pattern similar to the FVC and FEV_3 measurements. These results indicate that adaptation to ozone exposure occurred in these subjects and that loss of adaptation occurred within 4 days. No significant changes with exposures were observed in FEV_1/FVC, %, FEV_3/FVC, %, or forced expiratory flow between 25 to 75% VC (FEF_{25-75}).

The percentage decrease in FVC on the first exposure day showed a possible relationship with age or smoking history (pack–years). A negative linear relationship was observed [$r = -0.42$ for age ($P < 0.10$) and $r = -0.32$ for smoking history (NS)]; i.e., younger subjects tended to show more marked decreases in FVC.

TABLE 2
MEAN FORCED EXPIRATORY FUNCTION WITH TUKEY'S ANALYSIS

Test (Units)	Control mean	Days						
		M	TU	W	TH	F	M	TU
FVC	5.01	4.88	4.94	4.96	4.95	4.93	5.00	4.89
(liters)		(−3.89)**	(−2.26)	(−1.41)	(−1.72)	(−2.32)	(−0.37)	(−3.80)**
FEV_1	3.55	3.45	3.52	3.55	3.53	3.51	3.60	3.47
(liters)		(−2.76)	(−0.77)	(0.02)	(−0.55)	(−1.03)	(0.91)	(−2.04)
FEV_3	4.40	4.27	4.34	4.37	4.36	4.34	4.40	4.30
(liters)		(−4.12)**	(−2.13)	(−1.02)	(−1.49)	(−2.11)	(−0.22)	(−3.42)*
FEV_1/FVC	71	71	72	72	72	72	72	72
(%)		(−0.14)	(0.96)	(1.33)	(0.78)	(0.87)	(1.79)	(0.41)
FEV_3/FVC	88	88	86	88	88	88	88	88
(%)		(1.35)	(0.06)	(0.84)	(0.32)	(−0.06)	(0.71)	(−0.06)
FEF_{25-75}	2.71	2.36	2.52	2.51	2.56	2.52	3.08	2.80
(liters/sec)		(−1.44)	(−0.77)	(−0.79)	(−0.61)	(−0.77)	(1.54)	(0.36)

Note. The numbers in parentheses are the determined Tukey values.
* $P < 0.05$.
** $P < 0.01$.

Individually, there was wide variation in response patterns. Twelve of the twenty subjects showed adaptation with successive daily ozone exposures. Their ventilatory function on the fourth and fifth exposure days improved compared to the first exposure day. Some of the remaining eight subjects showed consistently small decrements in ventilatory function with exposure, while others never showed any decrement in ventilatory function.

Most of the subjects reported minor symptoms associated with exposure. Upper respiratory irritation, cough, or chest discomfort was experienced on 2 or more of the 6 exposure days by 6 of the 20 subjects. Symptoms did not predominate on any particular exposure day. Unlike previous ozone studies, no relationship was observed between the symptoms reported and decrement in pulmonary function.

DISCUSSION

This study evaluated subjects with mild chronic bronchitis and a history of cigarette smoking. The subjects, as a group, showed significant decrements in FVC and FEV_3 on the first day of exposure. The decreases were small, only -2.6% for FVC and -3.0% for FEV_3. On the second through fifth days of the sequential exposure, smaller, nonsignificant decreases in ventilatory function were observed. Following reexposure 4 days later, significant decreases again occurred in FVC and FEV_3 of about the same magnitude as seen on the first exposure day. The minor symptoms reported and the small decrements observed in pulmonary function should impose no more than minimal limitations to the subject's lifestyle.

The above results were compared with ozone exposure data from other studies to see if responses of subjects with chronic bronchitis differ from individuals with either normal or compromised ventilatory function. A recent study on normal, nonsmoking subjects was performed in our environmental chamber (Kulle *et al.*, 1982). That study used the same concentration of ozone and a similar protocol. Larger percentage decreases in ventilatory function were seen on the first and second exposure days (-8.0 and -8.1% in FVC, respectively). This decrement in ventilatory function became progressively smaller and nonsignificant on Days 3 through 5 of the sequential exposure. In contrast to the response of the subjects with chronic bronchitis, the normal subjects did not show a significant decrease in FVC with ozone reexposure 4 days later; only with reexpsoure 7 days later was a significant decrement in FVC obtained.

In an earlier study in our chamber (Kerr *et al.*, 1975), 10 smokers were found to be less sensitive than an equal number of nonsmokers in both subjective and objective reactions to a 0.5-ppm, 6-hr ozone exposure (FVC change $= +0.4\%$ for smokers versus -5.4% for nonsmokers). The smokers, as a group, showed no significant changes in ventilatory function with exposure, and only the younger smokers experienced symptoms.

These studies refute the idea that subjects with chronic bronchitis are more sensitive to ozone than are normal subjects. Subjects with chronic bronchitis appear to adapt sooner and lose adaptation more rapidly. However, they may be more sensitive to ozone than smokers with normal ventilatory function. The small

percentage changes observed in the present study would lead one to question if there is any clinical significance.

Studies on other groups of subjects with chronic respiratory diseases are not as easily compared because of differences in ozone concentration and protocol. Two recent studies have investigated the effects of ozone exposure in subjects with chronic obstructive pulmonary disease. These studies exposed patients with mild-to-moderate severe COPD to 0.12 ppm O_3 for 1 hr or 0.20 ppm O_3 for 2 hr, while performing 30 min of intermittent light exercise (Linn *et al.*, 1982; Solic *et al.*, 1982). A nonsignificant decrease in FVC (mean of 1.2%) was observed in the former study and no change was seen in FVC in the latter study. The mean ages were higher (62 and 56 versus 39), the mean FEV_1/FVC ratio was lower (57.5 and 50 versus 73%), and many of the subjects were on bronchodilator medication. The subjects participating in these two studies probably represented a wider variation of disease processes in that not all were current smokers (at least one subject in each study had never smoked), many reported wheezing as a chronic symptom, and not all had a chronic cough.

Individuals with asthma have been considered more sensitive to ozone than other groups of subjects. Greater variability of ventilatory airflow is seen in this population, and sensitivity to inhaled irritants is also observed. This was not supported in two exposure studies on asthmatic subjects. One study exposed subjects to 0.25 ppm O_3 for 2 hr with no exercise (Silverman, 1979). The group as a whole showed no significant decrement in ventilatory function, although one-third of the subjects demonstrated moderate, but nonsignificant changes in $\dot{V}_{50\%VC}$. The other study exposed subjects with asthma to 0.2 ppm O_3 for 2 hr with intermittant light exercise for a total of 60 min (Linn *et al.*, 1978). No significant changes in ventilatory function were seen.

The data of this reported study suggest that a negative correlation exists between the subjects' percentage decrease in FVC and age. Since Monday was the only day of Week 2 to show a significant decrease in FVC (Table 2), that day was chosen for examining any possible correlation. The correlation with age ($r = -0.42$) represents borderline significance, since an $r = -0.44$ would be significant at the 5% level. This negative correlation is further supported by a previous study involving 10 smokers with normal ventilatory function. Four of the five youngest smokers, aged 22 to 25, experienced symptoms of cough and chest discomfort with the 0.5-ppm, 6-hr ozone exposure; the remaining six subjects up to age 60 did not report these symptoms (Kerr *et al.*, 1975). The symptoms reported indicate that young healthy smokers appear to be more sensitive than older healthy smokers. These two studies with healthy smokers and smokers with chronic bronchitis suggest that a negative correlation exists between ozone sensitivity and age. If this observation is further verified, a physiological mechanism should be investigated.

Among all the groups of subjects studied, the normal nonsmoking individuals have the greatest response to ozone exposure (Kerr *et al.*, 1975; Horvath *et al.*, 1981; Linn *et al.*, 1982; Kulle *et al.*, 1982). The reported study demonstrates that smokers with chronic bronchitis are not as sensitive to ozone as healthy nonsmokers, but appear to be more reactive than smokers with normal ventilatory

function. Individuals with asthma apparently are not the most sensitive to ozone although studies have not exposed these subjects to comparable ozone protocols. Patients with mild-to-moderate severe COPD show nonsignificant changes in pulmonary function with exposure to lower O_3 concentrations than employed in this study. Further studies exposing subjects with various degrees of chronic obstructive pulmonary disease and asthma should be done employing comparable ozone protocols in order to determine if exaggerated sensitivity to ozone exists in these individuals.

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